

REMARKS**Introduction**

Receipt of a final office action dated January 9, 2008 is acknowledged. In the action, the claims are rejected for nonstatutory obviousness-type double patenting over claims 1-9 of US 5,851,999, and under 35 U.S.C. 103 as allegedly obvious over Lemischka (US Patent 5,185,438) ("Lemischka"), Matthews *et al.*, *PNAS*, 88:9026 ("Mathews") and Terman *et al.*, *BBRC*, 187:1579 ("Terman"), in view of Ullrich *et al.*, *Cell*, 61:203 ("Ullrich"), Ueno *et al.*, *Science*, 252:844 ("Ueno 1") and Ueno *et al.*, *JBC*, 267:1470 ("Ueno 2"). The specification is also objected to for formality reasons.

Status of the Claims

In this response, applicants amended claims 5 and 6. Support for the amended claims can be found throughout the specification, and in paragraph [0119] in particular.

Upon entry of these amendments, claims 5 and 6 will be pending. Applicants respectfully request reconsideration of these claims in view of the following remarks.

It is acknowledged that the foregoing amendments are submitted after final rejection. However, because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

Specification

The Examiner objected to the specification because the word "entirety" should be deleted from the paragraph beginning on page 1, line 4, and because the Abstract should only be a single paragraph. The Examiner also objected to the specification because the Brief Description of the Figures refers to Figures 11A and 11B and not figures 11-1 to 11-4, and does not include a SEQ ID NO. Incidentally, the Brief Description of the Figures was amended in a response filed on January 18, 2005 to recite "FIG. 11 (4 pages)." Nevertheless, applicants made the changes suggested by the examiner.

Formal Drawings

The examiner suggest submitting better copies of the figures prior to patent issuance. The examiner's suggested is noted.

Double Patenting Rejection

Claims 5-6 are rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-9 of U.S. Patent 5,851,999. Applicants request that the Examiner hold this rejection in abeyance until the subject matter of claims 5-6 is otherwise deemed allowable.

Rejection under 35 U.S.C. §103

Claims 5-6 are rejected as being obvious over Lemischka (U.S. 5,185,438), Matthews *et al.* ("Matthews") and Termen *et al.* ("Termen") in view of Ulrich *et al.* ("Ulrich") and Ueno *et al.* (including "Ueno-1" and "Ueno-2"). Applicants respectfully traverse this ground for rejection.

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* 127 S.Ct. 1727 (U.S. 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. While the Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), the Court held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "*important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed*", and specifically stated:

Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was *an apparent reason to combine the known elements in the fashion claimed* by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1721 at 1740-1741 (emphasis added).

In addition, The Supreme Court emphasized the significance of unexpected results to an obviousness analysis. The Court explained that “[t]he combination of familiar elements . . . is likely to be obvious when it does no more than yield predictable results.” *KSR* 127 at 1731. Here, there is no evidence that the results achieved by combining the cited references would predict that a truncated flk-1 consisting of amino acids 1 to 806 would have dominant negative activity. And where no reference suggests any advantage to the combination, the record only supports a finding that the results achieved by the present invention are unexpected and, therefore, not obvious.

Lemischka, Matthews and Terman purportedly describe cDNA sequences for wild-type Flk-1. None of these primary references, however, suggest the generation of truncated Flk-1 that has a functional extracellular and transmembrane domain. Moreover, none of these references suggests that expression of Flk-1 is specifically associated with endothelial cells or that a truncated Flk-1 could inhibit the cellular effects of VEGF binding.

And Ullrich, Ueno 1 and Ueno 2 do not remedy the defects of the primary references. They describe various other truncated receptor tyrosine kinases and show that early events in receptor tyrosine kinase signal transduction can be affected by such kinases in an artificial overexpression system. They do not, however, teach or suggest that truncated mutants would inhibit the biological response of endogenous receptors in a highly specific manner. Additionally, none of the references suggest that the truncated proteins are related to the Flk-1 receptor protein or that a truncated Flk-1 receptor protein would behave in a similar manner. Accordingly, one of skill in the art could not extrapolate the teachings of the truncated

tyrosine kinase mutants of Ullrich, Ueno 1 and Ueno 2 to Flk-1, especially in view of the state of the art at the time of filing the present application.

Furthermore, Ueno 1 even states that while kinase defective mutants of either insulin or EGF receptors inhibited function of their respective wild-type receptors, “the mutant receptors did not inhibit the autophosphorylation of wild-type receptors and the mechanisms by which the kinase defective mutants inhibited wild-type receptor function were not known.” Ueno 1 at 847. This indicates that the mechanism by which even related receptors function is dissimilar and even further supports that similar structure is not necessarily predictive of function. Thus, the references provide no reason for one skilled in the art to make truncated Flk-1 proteins of the present invention, or a cell line expressing this protein.

Nevertheless, in the interest of expediting prosecution, and without acquiescing to the office’s rejection, applicants amended claim 5 to recite that the truncated Flk-1 consists of amino acid sequences 1-806 of Flk-1. None of the cited references, either alone or in combination, would suggest making this particular truncated Flk-1, which retains 23 residues in the cytoplasmic domain.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this submission, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

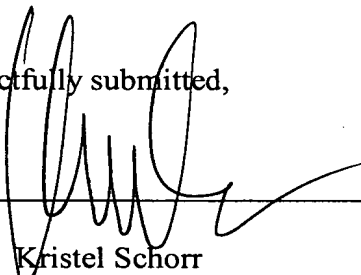
The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

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